

Beta-carotene in dermatology: does it help?

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S U M M A R Y

UV irradiation of the skin leads to the induction of free radicals, carcinogenesis, and skin aging, and thus the use of beta-carotene in humans as a chaperoning agent is discussed. In the photohemolysis model, beta-carotene protects against the phototoxic effects of porphyrins. Beta-carotene should be used in erythropoietic protoporphyria, photosensitive diseases, and to reduce the effects of phototoxic drugs. Its effects on aging skin and on actinic keratosis have not yet been sufficiently studied.

Introduction

Beta-carotene is a yellow pigment found in chlorophyll-containing plants, bacteria, and food. Among 600 known carotenoids, the substance is unique because two molecules of beta-carotene can combine to form retinol (vitamin A). Its consumption does not lead to hypervitaminosis A because of a feedback mechanism in the mucosa of the gut. Beta-carotene is available as a prescription drug for patients who suffer from erythropoietic protoporphyria, an inherited disease with abnormal photosensitivity in the skin. Beta-carotene is also known as an effective quencher of radicals, especially singlet oxygen, but also superoxide anion and hydroxy radicals; moreover, it is used to treat other diseases elicited or worsened by UV light, such as solar urticaria, polymorphic light eruptions, hydroa vacciniforme, Lupus erythematosus, and photoallergic drug reactions. Such treatment has resulted in only limited effect: sunburn-reaction is only minimally influenced.

In addition to the above, beta-carotene is used as a coloring agent in food, drugs, and cosmetics, where it is recognized as safe. When used as a micronutrient by sm-

okers over a longer period of time, care should be taken as epidemiological studies have shown the risk of lung cancer might increase. Individuals who consume over 30 mg beta-carotene daily for prolonged periods of time have subsequently been found to have high levels of beta-carotene in the blood and skin (hypercarotenoderma) and may develop a yellowing of the skin that is not considered a health problem, and is reversible on reduction of intake. Recent evidence suggests that beta-carotene may maintain immune response and collagen integrity.

Beta-carotene

Beta-carotene belongs to the carotenoids and is an important part of our physiological non-enzymatic defense mechanisms against radical stress. More than 600 carotenoids are known in plants and bacteria. We consume about 40 carotenoids daily by food, some of which can potentially yield vitamin A activity. About 12 of these are absorbed in the gut mucosa and can be mea-

K E Y W O R D S

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sured in plasma and tissues; α -carotene, β -carotene, lutein, zeaxanthine, β -cryptoxanthin, and lycopene are among the most common of these. About 30 to 60% of carotenoids are absorbed in the small intestine; the remainder is excreted (1).

Beta-carotene is the most abundant and most efficient precursor of vitamin A, which is a highly lipid-soluble unsaturated polyene dye and antioxidant found in the plasma. Moreover, vitamin A quenches the free radical singlet oxygen. Lycopene, another carotenoid, has no provitamin A function and is reputed to be more important than beta-carotene in UV-protection (2). Beta-carotene (a synonym to provitamin A) is derived from natural dietary sources such as carrots, tomatoes, spinach, sweet potatoes, other yellow and green vegetables, algae, and fruit. Table 1. In contrast, sources of vitamin A are animal foods such as egg yolk and liver. Beta-carotene is the most nutritionally active carotenoid. Gentle cooking generally improves utilization of beta-carotene in foods. It is best absorbed with fat, and further processed as a beta-carotene-lipoprotein-complex. In the gastrointestinal tract beta-carotene is metabolized to retinal by oxidative opening of a double bond by the enzyme 15,15'-Dioxygenase in intestinal cells or liver. Retinal is subsequently reduced to retinol; that is, vitamin A. Bilic acids work as detergents and help stimulate the metabolism of carotenoids. Fortunately, a negative loop in the gut prevents the development of intoxication. Once inside the body, beta-carotene is only partially converted to vitamin A; the rest is stored as beta-carotene. Accordingly, beta-carotene medication never leads to hypervitaminosis A (3). Both margarine and fruit drinks are often fortified with beta-carotene.

Being an unstable substance, beta-carotene is rarely used in cosmetic formulations (4). Other forms of vitamin A are commonly used in cosmetic formulations, mostly to normalize keratinization. The role of beta-carotene in nutritional uptake and as therapeutic medication continues to be of interest, however, and will be discussed later. Meanwhile, it is evident that in addition to being a safe source of vitamin A, beta-carotene plays important biological roles that are independent of its provitamin status.

Table 1. Carotenoids content in food.

Carotenoids	mg/100 g
Carrots	(mostly beta-carotene) 6.6
Sweet potatoes	6.0
Cress	5.6
Green kale	5.0
Spinach	4.9
Tomato	(mostly lycopene) 3.1
Mango	3.0
Melon	2.0
Apricot	1.5
Orange	0.1

Beta-carotene in acute UV damage

Beta-carotene is effective in light-sensitive skin diseases, such as polymorphic light eruption and especially in erythropoetic protoporphyria, a disease that causes sensitivity to light between 380 nm and 560 nm (5, 6). An experiment that has since become a classic shows the effect of beta-carotene in erythropoetic protoporphyria. Erythrocytes in suspension together with phototoxic porphyrine molecules are hemolyzed by UV irradiation. When beta-carotene is added in a second cuvette, erythrocytes hemolyze as well. This clearly shows that beta-carotene does not act as an optical filter system. When beta-carotene is added to the suspension with erythrocytes, the latter are protected. Beta-carotene is a free radical scavenger, quenching singlet oxygen and free radicals without damage to cells and tissue by conversion of irradiation energy into heat. This is explained by the fact that beta-carotene re-direct radiation energy by isomerization from the cis-carotenoid to a trans-carotenoid. Beta-carotene is superior to alpha-tocopherol in protecting from oxidation. Even if other substances are better scavengers for singlet oxygen, the advantage of beta-carotene is that it can be found in higher concentrations in plasma. As beta-carotene does not provide UV protection either by absorption of photons or UV reflection, sun protection creams and pigments still must be used (7).

Accordingly, beta-carotene reduced UV erythema only slightly in some studies (8–10) and had no effect on either the minimal erythema dose, or on the number of sunburn cells, sensitive markers of acute UV damage in keratinocytes (11, 12, 13). However, none of the free radical quenchers like vitamin E, vitamin C, or carotenoids are sunscreens. They have low sun protection factors in the UVA and less than SPF 4 in the UVB spectral range. Nevertheless, in vitro models of squamous cell carcinoma cells show that addition of beta-carotene inhibits the proliferation of these cells by the induction of a 70 kD heat shock protein (14). Heat shock proteins belong to the physiologically relevant proteins that protect cells from acute UV damage and protein misfolding (15).

Beta-carotene, aging, and skin carcinogenesis

Beta-carotene increases the immune defense by enhancing cytotoxicity of macrophages against tumor cells. It also increases lymphocyte production and T- and B-cell activity (16–19). By modulating immune defense, beta-carotene might have an impact on carcinogenesis.

In addition, beta-carotene may modulate skin carcinogenesis by a reduction of lipid peroxidation in human skin, either as a free radical scavenger or as specific lipoxygenase inhibitor. The substrates of lipoxygenases

are linoleic acid and arachidonic acid; the reaction produces leukotrienes, lipoxins, and physiologically active oxygenated fatty acids. Linoleic acid is one of the major components of membrane phospholipids of living cells that are damaged by reactive oxygen species, leading to pathological events and aging processes. In skin samples, inhibition of metabolites of linoleic acid was achieved using beta-carotene (20–23).

Cumulative UV exposure results in photoaging and increased risk of epithelial skin cancer. Free radical oxidative stress has been implicated in the pathogenesis of a variety of human diseases, including UV-induced skin cancer (24–27). Natural antioxidant defense mechanisms have been found to be defective in these patients. Disease progression seems to be retarded by supplementation of the natural antioxidant defenses. Potential antioxidant therapies include natural antioxidant enzymes and vitamins or synthetic agents with antioxidant activity (28, 29). Proteins exposed to free radical attack may fragment, cross-link, or aggregate. The consequences are ion-channel interference, cell receptor failure, failure of oxidative phosphorylation and, at the DNA level, base destruction and repair failure (24, 27).

The protective function of beta-carotene is explained as a quenching of singlet oxygen and inhibition of free radical reactions (10, 23). In animal models, beta-carotene protects against skin cancer induced by chemicals and UV irradiation (28, 29). In contrast, in animals undergoing tumor induction, beta-carotene application increased tumor formation (23). Additionally, since the 1980s beta-carotene has been proposed as a possible dietary preventive agent against cancer (1, 30). In epidemiological studies and clinical trials with beta-carotene as a dietary antioxidant, no consistent proof was obtained that it protects humans against skin cancer (29, 31, 32). Recently, it was shown that the daily use of oral beta-carotene (30 mg per day, $n = 1621$) for 4.5 years did not reduce the incidence of basal cell or squamous cell carcinoma; in contrast, daily sunscreen use resulted in a reduction in incidence of the latter (33).

Table 2. Present and possible future indications for beta-carotene oral use.

Erythropoietic protoporphyria
Polymorphic light eruption
Reduction of negative effects of phototoxic drugs
Hydroa vacciniforme
Solar urticaria
Lupus erythematosus
Vitiligo
Acne excoriée
Chloasma
Multiple dysplastic nevi
Skin aging

Beta-carotene and UV activation of dysplastic nevi

Patients with multiple dysplastic nevi (4–7% of the population) develop increased numbers of nevi starting in puberty (34). Patients complain about frequent excisions of those nevi that appear dysplastic, resulting in more body scars. The activation of such nevi depends on the amount of exposure to sunlight, the total number of melanocytic nevi, and their location on the body. In a dermoscopic study, UV irradiation with 2-fold minimal erythema doses on nevi resulted in becoming dark brown with faded borders. In addition, the hypopigmented areas of the nevi became smaller, and the pigment network faded and became less prominent. Overall, the irradiated nevi exhibited signs of activation (35). Moreover, immunodeficiency in HIV-infected patients and in renal transplant recipients promoted the occurrence of nevi. This supports the hypothesis that immunosuppression induced by UV irradiation also favors the development of new nevi (17, 19). UV light can significantly decrease the circulating plasma carotenoids. At the same time, UV light decreases antioxidant enzyme levels in the skin while increasing lipid peroxide levels (36). The clinical manifestations of solar damage, skin cancer, certain photodermatoses, and photoaging, are attributable in part to free radical production (26). The notion that immune reactions could be impaired by activated free radicals produced by UV irradiation has been ruled out (37). Feeding beta-carotene to animals did not alter susceptibility to UV immune suppression (38). This finding contrasts with those human studies in which beta-carotene dietary supplementation blocked the UV-induced depression of the overall immune response. This was shown in a model of UV-suppression of contact dermatitis and in tests for recall antigens (16, 17). Carotenoids may therefore possess some anticarcinogenic properties due to their interaction with and quenching of various radical species generated within cells (23).

Vitamin A and its analogues have long been known for their anticancer properties. The effect of topical 0.05% tretinoin lotion on atypical nevi showed a definite biological effect, such as fading or elimination of some atypical nevi (39). Oral consumption and topically applied vitamin A and its analogues have shown beneficial effects on squamous cell carcinoma (40), basal cell carcinoma (29), and melanoma (41). In contrast, a similar follow-up study in eleven patients treated with oral isotretinoin found no clinical or histological changes in atypical nevi (42). Carotenoids may have an effect on carcinogenesis either directly by their antioxidant activity or indirectly via conversion to retinoids which alter cellular differentiation and proliferation (10, 29).

Patients with multiple nevi profit from long-term beta-carotene supplementation only in highly UV-exposed body sites in respect to a slower development of new nevi and a reduction of dysplastic nevi in comparison to

controls (43). The effect of beta-carotene on the reduced development of new melanocytic nevi on the lower arm and feet might be explained by a retardation of the presumed manifestation of damaged cells in these UV-exposed body sites. An overall beneficial effect of beta-carotene on all body sites has not been shown.

Beta-carotene in cosmetic dermatology

Among carotenoids, canthaxanthine was available over the counter in the 1970s. The substance was sold as a photoprotectant and as a systemic skin colorant. The resulting color was bronze-like, and very popular. Retinopathy consisting of bright yellow, glistening crystalline deposits, in and around the maculae was observed after this medication. However, crystalline retinopathy is totally absent after long-term therapy with beta-carotene. Pure beta-carotene has been approved by the Food and Drug Administration as a color additive for use in foods, drugs, and cosmetics. It has also been approved as a safe dietary supplement and as a nutrient. Beta-carotene is much more bioavailable in its crystalline form than in its naturally occurring form.

Even though beta-carotene is very unstable, the substance is a popular additive in cosmetics for tanning. After topical application, the skin develops an orange tinge, which is highly valued by some users. Additionally, the substance is sometimes used as a "secondary" sunscreen, which may be added to cosmetics or primary sunscreens. "Secondary" sunscreens such as beta-carotene are characterized by a sun protection factor lower than 2.

After oral medication with beta-carotene, some users find the skin color highly acceptable, while others do not. In our study with long term beta-carotene medication 27% of 60 volunteers complained about this yellowish skin color (43). Beta-carotene is stored in several organs, including the skin; in particular the lines in palms and soles appear yellowish to brown. Sometimes the nasolabial fold and the perioral region appear yellowish (synonyms: aurantiasis cutis Baelz, carotenodermia, carrot icterus, xanthodermia). This hypercarotenodermia is reached when 30 mg/day or more have been taken for more than 4 weeks and is reversible after cessation of medication. The condition can be clearly differentiated from jaundice because the sclera remain white under beta-carotene medication (3). In hypercarotenodermia, the concentration of beta-carotene in stratum comeum is 5-fold higher than in normal skin. But even in normal skin, beta-carotene is one of the pigments responsible for skin color. The substance is also found in sebaceous gland cells and in the sebum.

Controlled studies with beta-carotene have to take into account the fact that the occurrence of hypercarotenodermia may not be acceptable to volunteers. As the study progresses, the yellowish discoloration of the skin makes the randomization "open" for both the patients and the physician. This might suggest some bias.

In pigmentation disorders (e.g., hypopigmentation:

vitiligo; hyperpigmentation: chloasma, acne excoriée) beta-carotene might be an additional option provided the patient does not object to the yellowing effect. In vitro data for beta-carotene showed protection of liposomes from UV-induced lysis, which is quite interesting for galenic reasons.

Beta-carotene protects dermal collagen from UV induced oxidation of proline. In contrast, in hairless mice, beta-carotene supplementation was not effective in preventing UVB-induced elastotic and collagen changes indicative of photoaging (44, 45). There are currently no controlled studies for beta-carotene and skin aging.

Is beta-carotene safe?

Beta-carotene is also a nutrient, thought to influence the process of carcinogenesis by chemoprotection in the early stages of tumor development. Extensive studies have been performed for beta-carotene, the vitamins A, C, and E, and the trace elements zinc, selenium, and calcium. Randomized controlled epidemiological studies showed no benefit from antioxidant vitamins (32). Moreover, the relative risk of dying from lung cancer or cardiovascular disease was increased in some of these studies (beta-carotene and retinol efficacy trial, CARET, (46); the alpha-tocopherol, beta-carotene (ATBC) cancer prevention study, (47)). The methodology of these studies was subsequently criticized because they included high-risk patients, such as smokers and asbestos workers (48). A third study (Physicians' Health Study) included 22,071 healthy male US physicians aged 40 to 84 who received 50 mg of beta-carotene on alternate days. No differences in cardiovascular diseases, malignant neoplasms, or the overall mortality were observed (49). In light of these studies, beta-carotene is not a risk factor in tumor progression. In contrast, epidemiological studies with dietary supplementation of beta-carotene (the CARET and ATBC studies) showed that such long-term supplementation with beta-carotene is an additional risk factor for smokers (31, 50). We therefore recommend that a balanced ratio of smokers to non-smokers be included in study groups in the future.

Conclusion: to use or not to use?

Beta-carotene is indicated in erythropoietic protoporphyria and other photosensitive diseases. Additionally, it might be used to reduce the negative effects of phototoxic drugs (3, 6). Table 2. For short vacation periods in regions with high UV exposure, beta-carotene (30 mg) is recommended, particularly in combination with alpha-tocopherol and ascorbic acid (Berlin Eilath study, 51). Smoking habits, alternative UV protection methods using textiles, and physical/chemical sunscreens should be discussed with the patient to ensure that long-term beta-carotene treatment is administered only after weighing the risks and benefits. In future research, it might be of interest to examine whether actinic keratosis and the aging skin respond to treatment with beta-carotene.

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